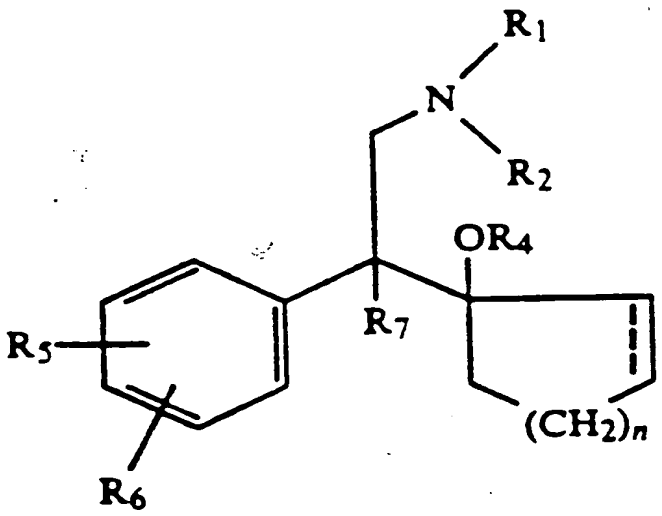
ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

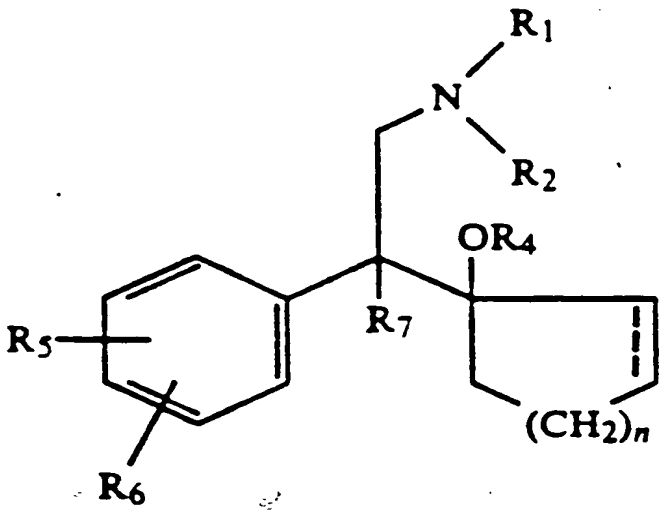
BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action

due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in Remington's Pharmaceutical Sciences, 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; The Pharmacological Basis of Therapeutics, 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in United States Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple dosing. The drugs of the structural formula are known in United States Patent Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in United States Pat. No. 4,327,725 issued to Cortese and Theeuwes and in United States Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying

side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37°C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while

simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing Figure 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing Figure 2 is an opened view of the dosage form of drawing Figure 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing Figure 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing Figure 1. In drawing Figure 1, a dosage form 10 is seen comprising a body member 11, which body 11 comprises wall 12, that surrounds and forms an internal area, not seen in drawing Figure 1. Dosage form 10 comprises at least one exit port 13 for connecting the exterior with the interior of dosage form 10.

The dosage form 10 of drawing Figure 1 illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

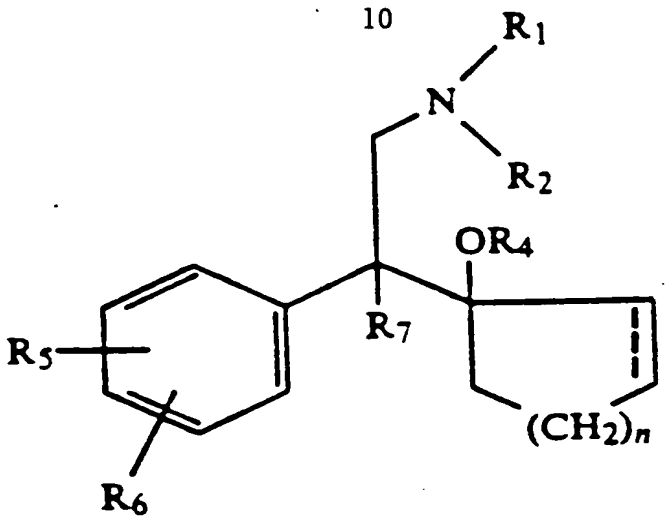
In drawing Figure 2, dosage form 10 of Figure 1 is seen in opened section. In drawing Figure 2, dosage form 10 comprises a body 11, a wall 12 that surrounds and defines an internal compartment 14. In drawing Figure 2, internal compartment 14 communicates through an exit passageway 13 with the exterior of dosage form 10.

Wall 12 of dosage form 10 comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall 12 is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment 14. Wall 12 comprises a composition that is substantially inert, that is, wall 12 maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form 10. The phrase, "maintaining its physical and chemical integrity," means wall 12 does not lose its structure and it does not change during the dispensing life of dosage form 10, except for possible leaching of one or more exit 13 passageway formed during operation of dosage form 10 or for leaching a water-soluble flux enhancers blended into wall 12. Wall 12 comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall 12, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-,di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl

content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripolmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

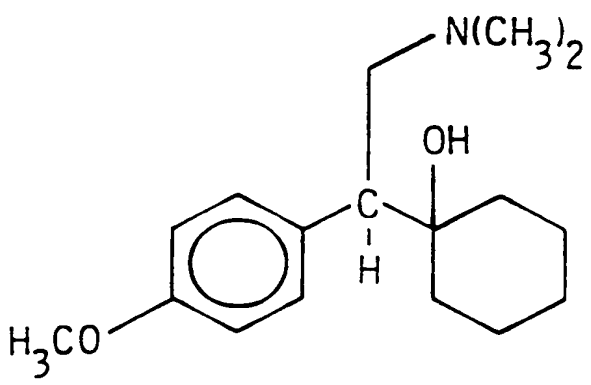
Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in Handbook of Common Polymers by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, OH.

Compartment 14 comprises a drug composition, identified as drug layer 15 which contains drug 16, identified by dots. Drug 16 comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, morepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug 16 in dosage form 10 is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug 16 for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in Current Therapeutic Research, Vol. 42, No. 5, pages 901 to 909 (1987).

Composition 15 comprising drug 16 may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt% to 25 wt% of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcelluose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes 17; a member selected from the group consisting of 0 wt% to 20 wt%

hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and hydroxybutylcellulose as represented by slanted line 18; a member selected from the group consisting of 0 wt% to 35 wt% of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinlycetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles 19; and 0 wt%, where wt% is weight percent, 35 wt% of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)_n\ H_2O$ wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square 20; as member selected from the group consisting of 0 wt% to 40 wt% of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles 20a. Composition 15 optionally comprises from 0 to 4.5 wt% of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition 15 is equal to 100 wt%, weight percent.

Compartment 14 comprises a displacement composition or push layer 21. Displacement composition 21 comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(O-CH_2CH_2)-_n$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line 22; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n\ H_2O$ wherein n is 50 to 62,000 and

comprises a 9,000 to 10,000,000 molecular weight and represented by triangle 23; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethyl-methylcellulose, alkali carboxymethyl-hydroxypropyl-methylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing Figure 2 as hexagonal 23a. The polymers in push layer 21 provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition 21 comprises optionally from 4 to 35 wt% of an osmotically active compound, also known as osmagent and represented by vertical line 24. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea, magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer 21 optionally comprises 0.5 wt % to 30 wt% of a cellulose polymer 25 represented by the letter v. Representative of cellulose polymer 25 comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt% to 5 wt% of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and

caprylic acid. The polymers are known in U.S. Pat Nos. 3,845,770; and 4,160,020; in Handbook of Common Polymers by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, OH.

Dosage form 10, a seen in drawing Figure 3 depicts another preferred manufacture provided by the invention. Dosage form 10, in drawing Figure 3, comprises an external coat on a the exterior surface of dosage form 10. Coat 26 is a therapeutic composition comprising 10 mg to 150 mg of drug 16, represented by dots 16. Exterior coat 26 provides instant drug 16 for instant therapy. Drug 16 is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat 26 optionally comprises polyethylene glycol or acetylated triglycerides. Coat 26 provides instant therapy as coat 26 dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug 16 to a drug receiving patient. Coat 26 provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form 10, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug 16 by the oral route, and in another embodiment, dosage form 10 comprising exterior and interior drug 16 can be sized and shaped for administering drug 16 by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug 16 is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug 16. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form 10 to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form 10, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway 13, or more than one passageway 13. The expression "at least one passageway"

includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall 12 in the fluid environment of use to produce at least one passageway in dosage form 10. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose, lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form 10. Dosage form 10 can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall 12 of osmotic dosage form 10 can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Volume 48, pages 451 to 454, (1959); and ibid, Volume

49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster ® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic ® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30°C. to 50°C. for up to a week to free dosage form 10 of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form 10 of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30°C. to 50°C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation techniques. The compositions are pressed into their individual layers in a Manesty ® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol /water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Vol. 48 pp 451-454 (1979); and, ibid, Vol. 49, pp 82-84 (1960). Other standard manufacturing procedures are described in Modern Plastics Encyclopedia, Vol 46, pp 62-70 (1969); and in Pharmaceutical Science, by Remington, 14th Ed., pp 1626-1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene

dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

EXAMPLE 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an

dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified

water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37°C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

EXAMPLE 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

EXAMPLE 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

EXAMPLE 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

EXAMPLE 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

EXAMPLE 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.